REMARKS

Claims 4 and 17 have been cancelled. Claims 1-3, 5-6, 8, 16-18, 21 and 23 have been amended. The amendments to the claims are supported throughout the application as filed. The specification has been amended merely to correct a typographical error, namely to replace the term "nanometers" with "nM" (nanomolar) as described throughout the rest of the application. No new matter has been added. Claims 1-3, 5-16 and 18-24 will be pending upon entry of this amendment.

Claim Rejections Under 35 U.S.C. § 102

Claims 1, 2, 16, and 17 are rejected as anticipated by the abstract of Sitter et al. (1998) *J. Amer. Soc. Nephr.* 9:2005-2012 (Sitter). The Examiner states that, "Sitter et al. teach of of a peritonieal (*sic*) dialysis fluid which contains D-glucose and a protein kinase C (PKC) inhibitor Ro 31-8220."

Claim 1, as presently amended, is directed to a method of treating permeability failure in a subject. The method includes introducing into said subject a peritoneal dialysis fluid which includes a specific inhibitor of PKC. Claim 16 is directed to a dialysis fluid that includes a specific inhibitor of PKC.

The Examiner cites Sitter as disclosing a PKC inhibitor. However, Sitter merely discloses exposing cultured cells to Ro 31-8220. Ro 31-8220, as used by Sitter, was known not to be a specific inhibitor of PKC in general, and, indeed, was known not to be specific to any single PKC isoform. In fact, Ro 31-8220 was known to inhibit several protein kinases other than PKC. Namely, Ro 31-8220 inhibits MAPKAP kinase-1β (also known as Rsk-2) more potently than it inhibits mixed PKC isoforms, and it also inhibits p70 S6 kinase (see Alessi (1997) *FEBS Lett.* 402:121-123, abstract, submitted herewith as Appendix A). As provided in the Alessi reference (Appendix A), Ro 31-8220 is not selective for PKC isoforms. The fact that Ro 31-8220 is not a specific PKC inhibitor has been confirmed in other studies (see, e.g., Guo et al. (1999) *Am. J. Physiol.* 276:C435-41, abstract (Appendix B)). Therefore, it cannot be said that Sitter's use of Ro 31-8220 constitutes a use of a specific inhibitor of PKC, regardless of Sitter's

(erroneous) statements to the contrary. Further, as the Examiner acknowledges, "Sitter et al. are silent to other inhibitors of PKC" (Office Action, page 3, paragraph 9). Therefore, Sitter does not describe methods of treatment using a specific inhibitor of PKC or a dialysis fluid containing a specific inhibitor of PKC, much less a specific inhibitor of a particular PKC isoform such as PKC β as is required by, e.g., claim 2.

Further, claims 1 and 2 are directed to treating permeability failure in a subject. In contrast, Sitter is concerned with the molecular mechanism for peritoneal prostanoid formation and peritonitis (see Sitter abstract, and page 2011). Nowhere does Sitter mention treating a subject having permeability failure.

For at least all of these reasons, Sitter does not anticipate the present claims. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-24 are rejected as unpatentable over Sitter et al. The Examiner asserts the following.

> Although Sitter et al. do not teach of other inhibitors of PKC it would have been obvious to one having ordinary skill in the art to substitute one PKC inhibitor for another since Sitter et al. are directed to prostaglandin E synthesis. Surely, the prior art reference of Sitter et al. render the instant invention obvious especially when the instant claims are only directed to generic methods of treating and to a peritonieal (sic) dialysis fluid. (Office Action, paragraph bridging pages 3-4).

The presently pending claims are directed to a method of treating permeability failure, a peritoneal dialysis fluid, and a method of making an improved peritoneal dialysis fluid, all of which include the use of a specific inhibitor of PKC. Claims 2, 3, 5-8, 18-21, and 24 require the use of a PKC inhibitor that is specific for one of several PKC isoforms, e.g., PKCβ. As discussed in detail above, Sitter does not teach or suggest treating permeability failure in a subject, nor does Sitter teach or suggest the use of a PKC specific inhibitor such as a PKCβ specific inhibitor. Rather, Sitter describes exposing cultured cells to Ro 31-8220, which is known to be non-specific kinase inhibitor. In addition, as Ro 31-8220 is known in the art to be toxic *in vivo*, one would not have been motivated to make a peritoneal dialysis fluid, or to treat permeability failure in a subject, with Ro 31-8220.

Moreover, even if Sitter did disclose the use of a PKC specific inhibitor in a dialysis fluid (which it does not, for the reasons discussed hereinabove), Applicant disagrees with the Examiner that "it would have been obvious to one having ordinary skill in the art to substitute one PKC inhibitor for another". PKC isozymes are known to play distinct, and in some cases, opposing roles in the transduction of intracellular signals. Thus, a skilled artisan would surely not be motivated to substitute one PKC isozyme specific inhibitor for another.

Therefore, because Sitter neither discloses nor suggests the presently pending claims, Applicant respectfully requests that this rejection be withdrawn.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant submits that all the claims are in condition for allowance. Enclosed is a $55 check for a Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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Version with markings to show changes made pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

In the specification:

Paragraph beginning at page 2, line 5, has been amended as follows:

--In a preferred embodiment, an inhibitor of PKC is included in the peritoneal dialysis fluid. The inhibitor is preferably a specific inhibitor of PKC. The inhibitor can be an inhibitor of a PKC β, e.g., β1 or β2, γ, δ, or other isoform. The inhibitor can be, for example, a bis (indolyl) maleimide, for example, the PKC β inhibitor LY333531, which is described in Ishi et al. (1996) *Science* 272:728-731, hereby incorporated by reference. LY333531 can be present in the dialysis fluid at about 1-1,000, 5-750, 20-500, but more preferably 50-500 [nanometers]nM.--

Paragraph beginning at page 3, line 6, has been amended as follows:

-- In a preferred embodiment, an inhibitor of PKC is included in the peritoneal dialysis fluid. The inhibitor is preferably a specific inhibitor of PKC. The inhibitor can be an inhibitor of a PKC β, e.g., β1 or β2, γ, δ, or other isoform, or combinations thereof. The inhibitor can be, for example, a bis (indolyl) maleimide, for example, the PKC β inhibitor LY333531. LY333531 can be present in the dialysis fluid at about 1-1,000, 5-750, 20-500, but more preferably 50-500 [nanometers]nM.--

In the claims:

Claims 4 and 17 have been cancelled.

Claims 1-3, 5-6, 8, 16-18, 21 and 23 have been amended as follows:

--1. (Amended) A method of treating permeability failure in a subject, comprising: introducing into said subject a peritoneal dialysis fluid which includes [an] a specific inhibitor of a PKC, thereby treating said subject.

2. (Amended) The method of claim 1, wherein said specific inhibitor is a specific inhibitor of PKC β.

3. (Amended) The method of claim [2]1, wherein said specific inhibitor is selected from the group consisting of: [an]a specific inhibitor of a PKC β, [an]a specific inhibitor of PKC γ, and [an]a specific inhibitor of PKC δ.

4. (Cancel) The method of claim 2, wherein said inhibitor is an inhibitor of PKC β.

5. (Amended) The method of claim [4]1, wherein said specific inhibitor is an inhibitor of PKC β1.

6. (Amended) The method of claim [4]2, wherein said inhibitor is a bis (indolyl) maleimide.

8. (Amended) The method of claim 7, wherein said LY333531 is present in said dialysis fluid at about 1-1,000 [nanometers]nM.

16. (Amended) A peritoneal dialysis fluid comprising [an] a specific inhibitor of a PKC.

17. (Cancel) The dialysis fluid of claim 16, wherein said inhibitor is a specific inhibitor of PKC.

18. (Amended) The dialysis fluid of claim [17]16, wherein said specific inhibitor is an inhibitor of PKC β.

21. (Amended) The dialysis fluid of claim 20, wherein said LY333531 is present in said dialysis fluid at about 1-1,000 [nanometers]nM.

23. (Amended) A method of making an improved peritoneal dialysis fluid, comprising: providing a peritoneal dialysis fluid; and
adding to that fluid [an] a specific inhibitor of a PKC, to thereby provide an improved dialysis fluid.--